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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,693	02/02/2001	Mike A. Clark	PHOE-0060	9010

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,693	CLARK ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,27 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7,27 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 3-5, 8-26, 28-30, and adds new claims 31-36 which are related to claims 1-2, 6-7, 27 and are not new matters.

Accordingly, Claims 1-2, 6-7, 27, 31-36 are examined in the instant application.

MISCEALLANEOUS

Applicant's submission of the Declaration by Mike Clark is acknowledged.

REJECTION UNDER 35 USC 103, NEW REJECTION

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 6-7, 27, 31-36 are rejected under 35 USC 103(a) as being obvious over US 5,804183 in view of Takaku, H et al, 1995, Jpn. J Cancer Res, 86: 840-846, IDS# AM, in paper No:6, on 06/19/01, Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, and Oyanagi, K et al, 1986, Tohoku J Exp Med (Japan), 148 (4): 385-91.

Claims -2, 6-7, 27, 31-36 are drawn to a method for identifying a cancer patient susceptible to arginine deprivation therapy, comprising detecting, in a cancerous tumor sample of a cancer patient, the presence or absence of argininosuccinate synthetase protein, wherein the absence of argininosuccinate synthetase protein in said sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, and the presence of argininosuccinate synthetase protein in said sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy. Said method further comprises detecting the presence of argininosuccinate synthetase protein in a non-cancerous sample of the corresponding tissue from the cancer patient, wherein the absence of argininosuccinate synthetase protein in said non-cancerous and cancerous tumor samples is indicative of a cancer patient who is a candidate for arginine deprivation therapy, wherein the presence of argininosuccinate synthetase protein in said non-cancerous sample and the absence of argininosuccinate synthetase protein in said cancerous sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, and wherein the presence of argininosuccinate synthetase protein in said cancerous sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy. The detection of argininosuccinate synthetase protein is by using ELISA, or an antibody specific for argininosuccinate synthetase protein or a portion thereof. The antibody has a detectable label, which is radioactive, fluorescent or chromomorphic, or an enzyme or has a visible color. The detectable label could be I^{131}, I^{125}, C^{14}, S^{35}, P^{32}, or P^{33}, or fluorescein, phycolipoprotein, or tetrarhodamine isothiocyanate.

US 5,804183 teaches a method for treating cancer or carcinoma or melanoma in a mammal, comprising administering arginine deaminase to reduce arginine level in said mammal, wherein said cancer is deficient in argininosuccinate synthetase (claims 7-10).

US 5,804183 does not teach a method for identifying a cancer patient susceptible to arginine deprivation therapy, comprising detecting, in a cancerous tumor sample of a cancer patient, the presence or absence of argininosuccinate synthetase protein, wherein the absence of argininosuccinate synthetase protein in said sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, and the presence of argininosuccinate synthetase protein in said sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy. US 5,804183 does not teach that said method further comprises detecting the presence of argininosuccinate synthetase protein in a non-cancerous sample of the corresponding tissue from the cancer patient, wherein the absence of argininosuccinate synthetase protein in said non-cancerous and cancerous tumor samples is indicative of a cancer patient who is a candidate for arginine deprivation therapy, wherein the presence of argininosuccinate synthetase protein in said non-cancerous sample and the absence of argininosuccinate synthetase protein in said cancerous sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, and wherein the presence of argininosuccinate synthetase protein in said cancerous sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy. US 5,804183 does not teach that the detection of argininosuccinate synthetase protein is by using ELISA, or an

antibody specific for argininosuccinate synthetase protein or a portion thereof. US 5,804183 does not teach that the antibody has a detectable label, which is radioactive, fluorescent or chromomorphic, or an enzyme or has a visible color. US 5,804183 does not teach that the detectable label could be I^{131}, I^{125}, C^{14}, S^{35}, P^{32}, or P^{33}, or fluorescein, phycolipoprotein, or tetrarhodamine isothiocyanate.

Sugimura, K, et al teach that AD is a potent growth inhibitor of some but not all tumor cell lines *in vitro*. Sugimura, K, et al further teach that because AD catalyses the direct conversion of L-arginine to L-citrulline, the AD sensitivity of various tumor cells is attributed to the reduced level of argininosuccinate synthetase gene expression, as shown in all five melanoma cell lines tested that are sensitive to AD treatment (abstract, p.194, second column, under Discussion). In addition, Sugimura, K, et al also teach that human peripheral blood lymphocytes are highly sensitive to the cell growth inhibitory activity of AD *in vitro*, because of their extremely low level of expression of the ASS gene (two to three copies per cell) (p.191, second column, last three lines bridging p.192). Sugimura, K, et al further teach that L-arginine is essential for the survival of many mammalian cells and is synthesized from L-citrulline by argininosuccinate synthetase and argininosuccinate lyase (figure 1 on page 191 and second column of page 191).

Takaku, H et al teach inhibition of growth of hepatoma in mice, using arginine deiminase (AD), and that said inhibition is caused by depletion of essential nutrient L-arginine by AD, and blocking of the polyamine biosynthesis pathway (abstract, page 843-844).

Oyanagi, K et al teach that argininosuccinate synthetase activities in the liver tissue patient with hepatoma are reduced as compared to normal liver control tissue.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to identify a cancer patient susceptible to arginine deaminase treatment, by detecting the presence or absence of argininosuccinate synthetase, because of the following reasons: 1)) Not all tumor cells are susceptible to AD treatment, as taught by Sugimura, K, et al, 2) Cancer patients having reduced argininosuccinate synthetase such as hepatoma and melanoma could be treated with AD, as taught by Takaku, H et al, and US 5,804183, wherein inhibition of cancer growth is caused by depletion of essential nutrient L-arginine by AD, as taught by Takaku, H et al, and 3) the AD sensitivity of various tumor cells is attributed to the reduced level of argininosuccinate synthetase gene expression, as shown in all five melanoma cell lines tested that are sensitive to AD treatment, as taught by Sugimura, K, et al. It would have been obvious to detect the argininosuccinate synthetase using a labeled specific antibody, rather than detecting argininosuccinate synthetase activity, detection of a protein using a specific antibody is well known in the art, and because one would have expected to obtain the same results. It would have been obvious to use a detectable label, which is radioactive, fluorescent or chromomorphic, or an enzyme or has a visible color, or I^{131}, I^{125}, C^{14}, S^{35}, P^{32}, or P^{33}, or fluorescein, phycolipoprotein, or tetrarhodamine isothiocyanate because these labels are well known and are commonly used in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

June 30, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER